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Synthesis of Nucleoside Analogs for Preparation of Phosphinate DNA

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Introduction

Antisense oligonucleotides that inhibit the synthesis of proteins are currently an area of interest in medicinal chemistry[1]. Antisense oligonucleotides bind to a complementary sequence of mRNA, interfering with the translation of mRNA into the corresponding protein. This process results in inhibition of the expression of specific genes[2]. Therefore, antisense oligonucleotides can potentially be used for disease treatments, for example, by selectively inhibiting oncogenes or viral RNA expression[1].

Natural DNA/RNA oligonucleotides are readily hydrolyzed by nucleases in the cell[3]. Phosphorus-oxygen bonds in the backbone of oligonucleotides are the specific sites of nuclease cleavage[1]. Several studies have developed strategies to produce nuclease resistant analogs[3, 4]. Currently, the most common strategies of creating hydrolytically stable antisense oligonucleotides are phosphorothiates (that contain phosphorus-sulfur bonds instead of phosphorus-oxygen bonds) or methylphosphonates (that contain phosphorus-methyl bonds instead of phosphorus-oxygen bonds)[3, 4]. However, such analogs have exhibited lower binding affinity with mRNA.

Our long term goal is to synthesize analogs where both phosphorus-oxygen bonds in the backbone are replaced with phosphorus-carbon bonds (phosphinate analogs) (Figure 1). Phosphinate oligonucleotides synthesized from these analogs should be resistant to cellular nucleases and effective for antisense therapy, as well as allow exploration of the biochemical mechanism of nuclease activity.

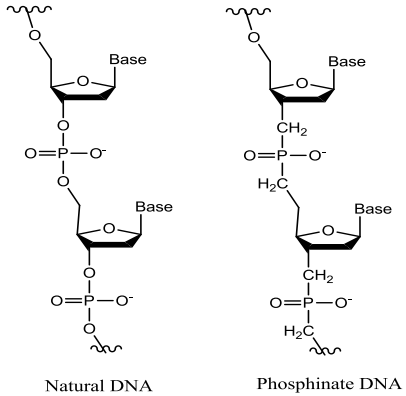
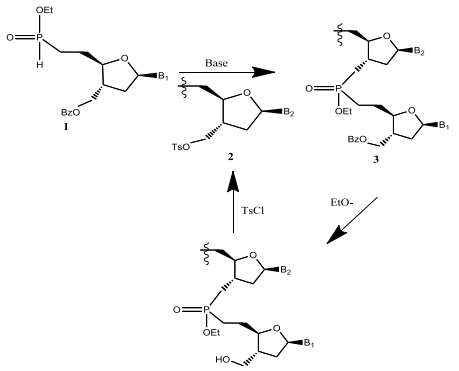


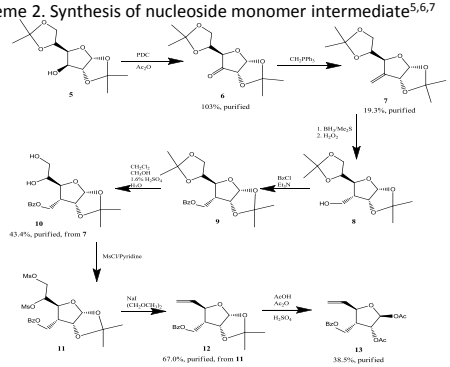
Figure 1. Natural DNA and Phosphinate analog

Scheme 1. General strategy for the synthesis of phosphinate DNA



The project

Scheme 2. Synthesis of nucleoside monomer intermediate[5,6,7]



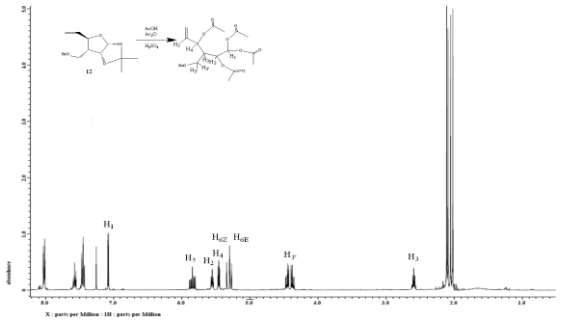


Figure 3. ^{1}H-NMR spectra of the side product of the diacetylation reaction. Sulfuric acid present may have opened up the ring as shown.

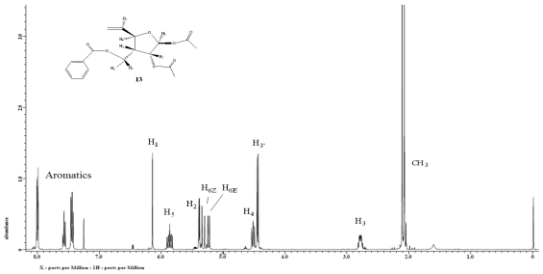


Figure 2. ^{1}H-NMR spectra of the diacetate (**13**).

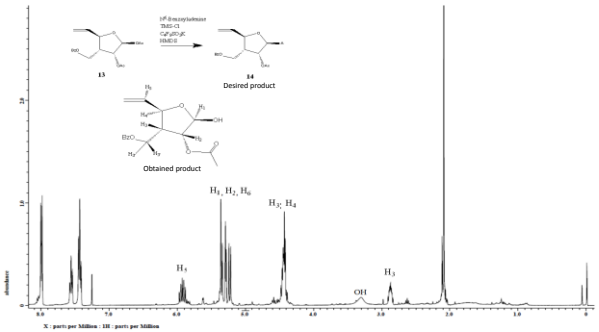
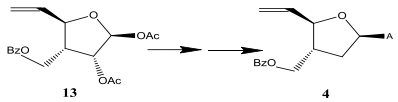


Figure 4. ^{1}H-NMR spectra of 3,5,6- Trideoxy-5,6-didehydro-3-[(benzoyloxy)methyl]-2-O-acetyl-β-D-allofuranose. The appropriate acetyl group has been removed, but the base has not been attached. This result may be due to presence of residual water or outdated reagents.

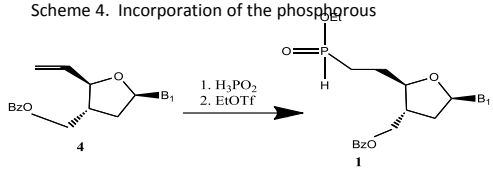
Future Research

Perform the following schemes:

Scheme 3. Completing the synthesis of the nucleoside



Scheme 4. Incorporation of the phosphorous



Acknowledgements

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